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Secondary Isotope Effects of Nucleophilic Vinylic Substitution

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SECONDARY ISOTOPE EFFECTS OF NUCLEOPHILIC VINYLIC SUBSTITUTION

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ABSTRACT

Mechanistic investigations have shown that nucleophilic vinylic substitution at sp^2 carbon occurs by a variety of mechanisms. The vinyl cation and addition-elimination mechanisms are the extremes represented by leaving group dissociation followed by attack by the nucleophile and vice-versa. It has been proposed that a continuum exists between these mechanistic extremes with a concerted process (leaving group departure and nucleophile attack are synchronous) in the middle of this continuum.

The use of secondary isotope effects is suggested as an investigative tool to locate where along the continuum a particular substitution reaction lies. A distinct difference is observed between the previously reported secondary isotope effects for vinyl cations (small and positive ~ 1.05 to 1.20) and the results we obtained for addition-elimination substitutions. 2-choloro-1,1-dicarbomethoxyethylene was used as the substrate because of its strong electron withdrawing substituents on the β-carbon. Aniline, 2,6-dimethylaniline, m-anisidine, and p-bromoaniline showed effects where k_H/k_D = .73, .79, .74, and .82, respectively, when reacted with the substrate and its deuterated analogue.

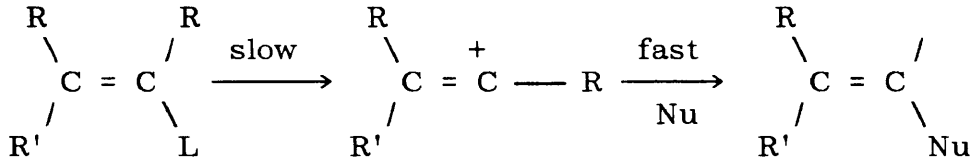
The use of transition metal complexes as nucleophiles was also investigated. Complexes such as $Pt[(Ph_3)]_4$ undergo an oxidative addition as they substitute for a leaving group at a vinylic carbon. Secondary isotope effects for reactions of the platinum complex with substrates were observed and found to be highly inverse which may suggest that another mechanism is operating.

SECONDARY ISOTOPE EFFECTS OF NUCLEOPHILIC VINYLIC SUBSTITUTION

It has been proposed that the replacement of substituents at vinylic carbon atoms proceeds via a variety of mechanism.[1, 2, 3] There are two fundamental interactions and their timing determines the mechanism. The first is attack by the nucleophile and the second is cleavage of the carbon to leaving group bond.

If the leaving group departs first, a vinyl cation if formed.[4] Subsequent addition of the nucleophile in a rapid second step results in formation of the substitution product.

FIGURE 1



This vinyl cation mechanism can be considered analogous to S_N1 substitution at saturated carbon where a carbocation is also formed.

If leaving group departure and attack by the nucleophile occur simultaneously, then the substitution is considered to be a concerted process.

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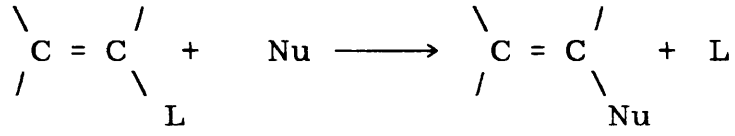
[1]Z. Rappoport, Adv. Phys. Org. Chem., 1969, **7**, 1.

[2]G. Modena, Accounts Chem. Res., 1971, **4**, 73.

[3]P.J. Stang, Z. Rappoport, M. Hanack, and L.R. Subramanian, "Vinyl Cations," Academic Press, New York, 1979.

[4]P.J. Stang, Z. Rappoport, M. Hanack, and L.R. Subramanian, "Vinyl Cations," Academic Press, New York, 1979.

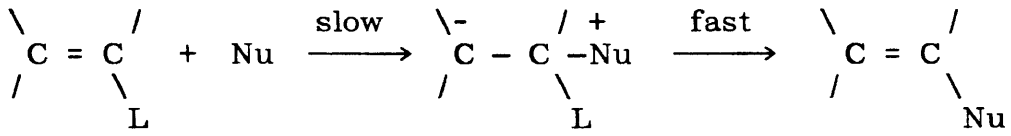
FIGURE 2



As with S_N2 substitution at a saturated carbon, leaving group bond breaking and nucleophile bond formation are synchronous. This single step mechanism is also known as direct substitution.

Vinylic substitution differs from its alphatic analogues in the case where the nucleophile can add to the substrate in a distinct first step.[5] A bond is formed from the electrophilic carbon under attack to the nucleophile. The π-electrons of the double bond are displaced to the β-carbon forming a zwitterion if the nucleophile is neutral, or a carbanion if the nucleophile is negative. Electron-withdrawing substituents on the β-carbon encourage formation of the carbanionic species and substrates with this general structure are referred to as activated. In a second, rapid step the leaving group is expelled and the π electrons return to reform the double bond.

FIGURE 3



This mechanism is referred to as an "addition-elimination," or a multi-step route.

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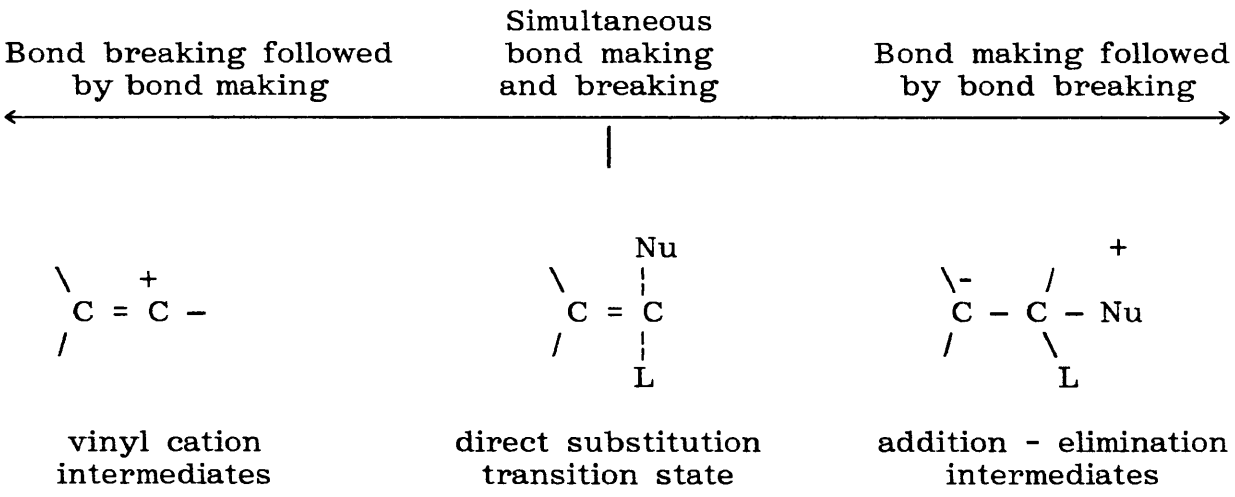
[5]Z. Rappoport, Accounts Chem. Res., 1981, **14**, 7.

There are several competing reactions:[6] elimination to an alkyne; addition to a saturated compound; α,α elimination - addition via a carbene; and α, β elimination - addition via an allene. However, nucleophilic vinylic substitution in its strictest sense can be limited to the three previously mentioned mechanisms or some variation along the continuum of mechanisms represented by vinyl cations to direct substitution to addition elimination.

FIGURE 4



Rappoport [7] has proposed that a continuum exists between the mechanistic extremes of the vinyl cation and the addition-elimination routes. The transition state or intermediate is variable and will occur as a function of the nucleophile, the substrate and its substituents, and the solvent. Although an exact relationship between mechanism and these variables is not known, there is considerable evidence to form a

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[6]Z. Rappoport, Adv. Phys. Org. Chem., 1969, **7**, 74.

[7]Z. Rappoport, Accounts Chem. Res., 1981, **14**, 9.

reliable correlation and a model system that will predict the correct mechanism. Stereochemistry, element effects and secondary isotope effects are used as evidence to suggest the appropriate mechanism.

STEREOCHEMISTRY

As with saturated analogues, the stereochemistry of solvolytic substitution at vinyl carbons is extremely insightful in determining the mechanism of substitution. Since chirality is not available generally as a mechanistic tool, the ratio of E and Z isomers in the product is compared to the reactant. The relationship of the β-substituents with the leaving group and the nucleophile indicate the stereochemistry of the substitution. If the product gives a complete stereoconvergence it can be hypothesized that a linear vinyl cation has been formed. Subsequent attack by the nucleophile occurs from any direction to give a product ratio that is only dependent on the relative energies of the products. In cases where an α- or β- substituent could stabilize the intermediate vinyl cation, complete stereoconvergence has been observed. Sherrod and Bergman[8] observed that cyclopropyl stabilized systems such as 1 - cyclopropyl - 1 - iodopropene gave the same ratio $^{E}/_{Z}$ in the product regardless of the configuration of the starting material.[9, 10]

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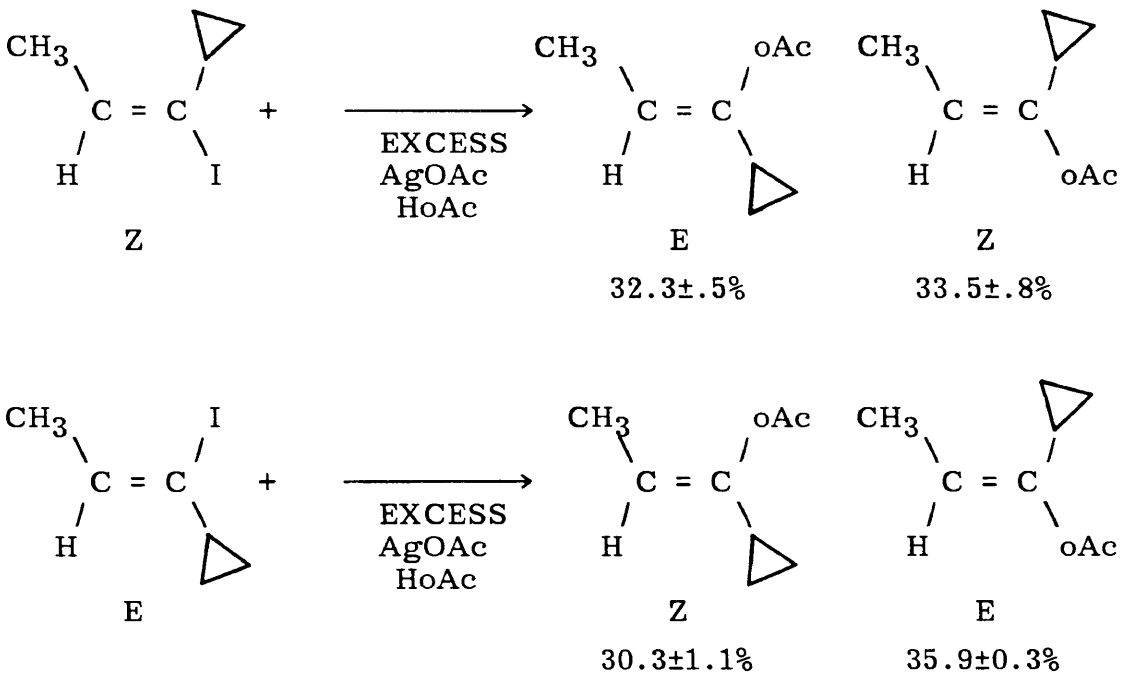
[8]S.A. Sherrod and R.G. Bergman, J. Am. Chem. Soc. **93**, 1925 (1971).

[9]S.A. Sherrod and R.G. Bergman, J. Am. Chem. Soc. **93**, 1925 (1971).

[10]D.R. Kelsey and R.G. Bergman, J. Am. Chem. Soc., **93**, 1941 (1971).

FIGURE 5

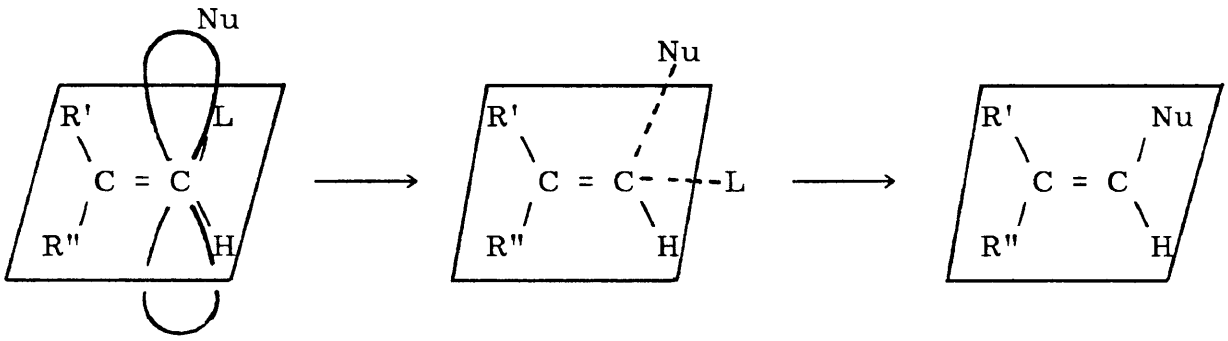


This strongly suggests that both the E and Z isomers lose iodide in a slow rate determining step to form an identical planar cyclopropyl-stabilized vinyl cation intermediate. Addition of the nucleophile results in a constant ratio of E to Z isomer in the product.

Several examples of stereoconvergence have been observed for nucleophilic vinylic substitutions proposed to proceed by a vinyl cation. In many of these cases there is a slight preference for one isomer over the other. This is explained generally by the interaction of a β-substituent and the nucleophile. Large steric hinderance might induce the nucleophile to attack preferentially from the opposite side, while hyperconjugation might attract the nucleophile to the same side as the pertinent substituent.

In the case of the single step mechanism complete or near complete retention of configuration is observed.[11, 12] Attack of the nucleophile occurs perpendicular to the plane of the vinyl group. As the bond from the nucleophile to the vinylic carbon forms, the bond to the leaving group is breaking and the leaving group departs from the opposite side of the plane.

FIGURE 6



The substitution occurs with retention of configuration because the nucleophile replaces the leaving group before the carbon atom can rotate. Several examples of substitutions with greater than 98 percent retention of configuration have been observed. These include a variety of substrates, nucleophiles, and configurations.

There are examples of both activated and deactivated substrates as well as moderate to excellent nucleophiles that give nearly complete retention of configuration. This would already appear to indicate that

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[11]D.Dodd, M.D. Johnson, B.J. Meeks, D.M. Titonmarsh, K.N.V. Duong, and A. Guademer, J. Chem. Soc., Perkin Trans. 2, 1261 (1976).

[12]S.I. Miller, Tetrahedron, **33**, 1211 (1977).

Table 1

REACTIONS GIVING >98% RETENTION OF CONFIGURATION

$$p\text{-}O_2NC_6H_4CH = CHBr + PhS^- \longrightarrow {}^{13}$$

$$PhCH = CHBr + PH_2P^- \longrightarrow {}^{14}$$

$$ClCH = CHCO_2Et + \underset{\diagup \quad \diagdown}{\overset{NH}{CH_2\text{-}CH_2}} \longrightarrow {}^{15}$$

$$ClCH = CHCN + EtS^- \longrightarrow {}^{16}$$

there is a spectrum or continuum of mechanisms that can occur in vinylic substitution. If substrates that would generally be associated with addition-elimination because of their activating substituents give results that indicate they actually proceed via a direct substitution mechanism because of its near complete retention of configuration then it appears reasonable to hypothesize a mechanism between these two extremes with an infinite number of distinct possibilities along the mechanistic coordinate.

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[13]G. Marchese, G. Modena, and F. Naso, Tetrahedron **24**, 663 (1968).

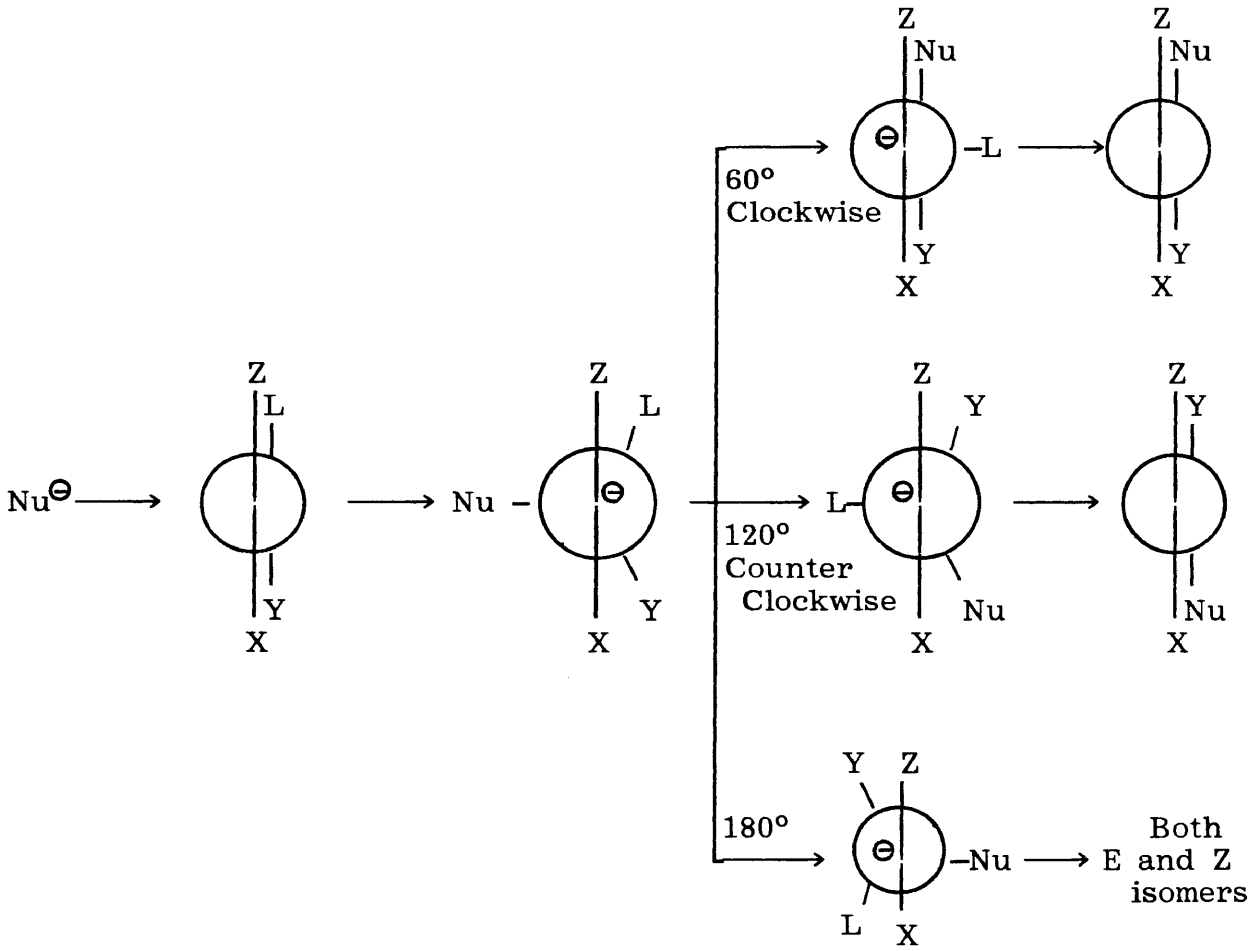
[14]A.M. Aguiar and D. Daigle, J. Am. Chem. Soc., **86**, 2299 (1964).

[15]J. Biougne, F. Theron, and R. Vessiere, Bull. Soc. Chim. Fr., 2703 (1975).

[16]W.E. Truce and M.L. Gorbaty, J. Org. Chem., **35**, 2113 (1970).

Substitution proceeding by the addition-elimination mechanism leads to a variety of stereochemical possibilities.[17] In the slow, rate-determining step the nucleophile binds to carbon and the intermediate anionic species is produced. If the intermediate rotates 120° in a counter clockwise fashion the product will be inverted. If the intermediate is allowed to rotate 180° or for an extended period of time, steroconvergence will result.

FIGURE 7



[17]Z. Rappoport, Accounts Chem. Res., 1981, **14**, 8.

Using stereochemistry as an investigative tool is a good starting point for determining the likely mechanism. Substitution proceeding by a vinyl cation should show a large degree of racemization, while those substitutions occurring in a concerted process will maintain near complete retention of configuration. If the reaction follows an addition-elimination route a variety of stereochemistries is observed dependent upon rotation about the carbon-carbon double bond and stability of the intermediate.

ELEMENT EFFECTS

Element effects in substitutions are determined by measuring the relative reactivities of various vinyl halides. Electronegativity and carbon to halide bond strength effect the rate of bond breaking to the leaving group. This offers further insight into which mechanism is functioning.

In the case of the vinyl cation mechanism, cleavage of the carbon to halide bond is the rate-determining step and so a great deal of information can be obtained from examining the element effects. Observed element effects correlate well with carbon to halide bond strength data. These examples thus exhibit rates where $K_{Br} >> K_{Cl} >> K_F$.

FIGURE 8

1,3-ditert-butyl-3-phenyl-1-chloropropadiene ^{18} ⟶

1,3-ditert-butyl-3-phenyl-1-bromopropadiene ⟶

$$\frac{k_{Br}}{k_{Cl}} = 56 \text{ @ } 35°C$$

The weaker carbon to bromine bond breaks more easily and substitution proceeds faster than with chlorine. The leaving group's ability to accommodate negative charge is proportional to its rate of departure. This has led to the use of super leavers such as tosylate, brosylate and triflate. Triflates are known to be 10^4 - 10^5 times more reactive than the corresponding arene sulfonates[19] and therefore some 10^8 - 10^9 times faster than alkyl halides.[20] Using these excellent leaving groups, vinyl cations are more readily generated.

Stang and Summerville[21] prepared and investigated the solvolytic substitution of acyclic vinyl triflates for the first time. Cis-2-buten-2-yl triflate solvolyzes at 76° ($k_{76°}$ = 2.3 X 10^{-5} sec^{-1}) to give dimethylacetylene (58%), methylallene (9%), and 2-butanone (33%). The reaction proceeds via a unimolecular ionization with a vinyl cation as an intermediate.

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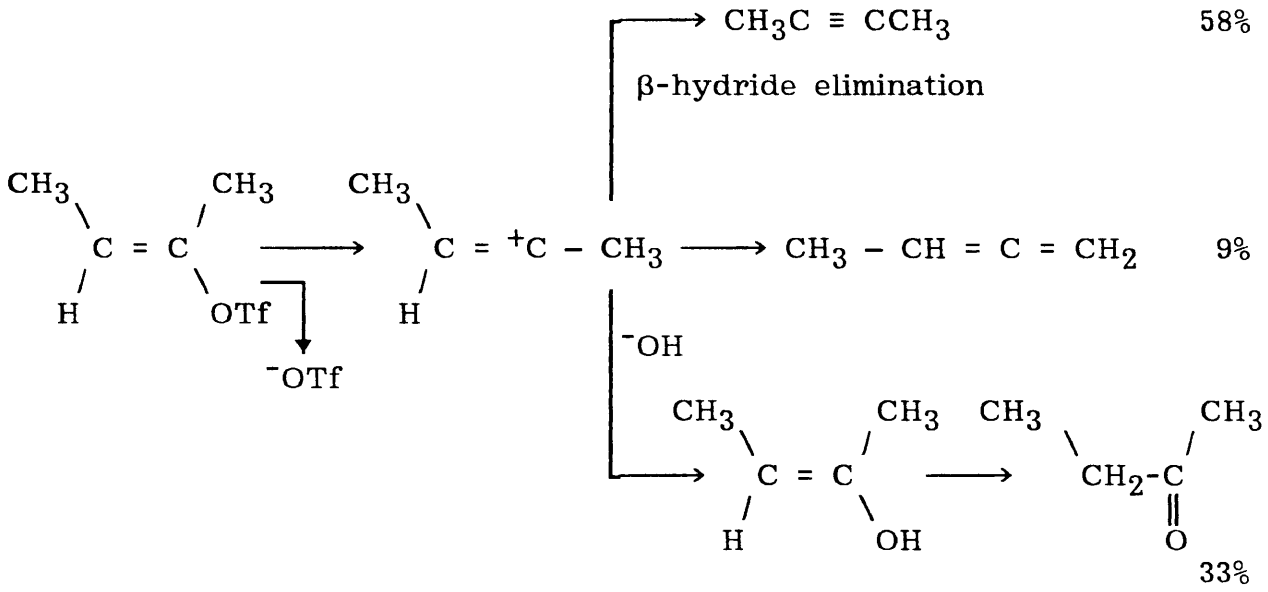
[18]M.D. Schiavelli, R. Gilbert, W. Boynton, and C. Bosewll, J. Am. Chem. Soc., **94**, 5061 (1972).

[19]M. Su, W. Sliwinski, and P. Schleyer, J. Am. Chem. Soc., 91, 5385 (1969).

[20]R. Hansen, J. Org. Chem., **29**, 4322 (1965).

[21]P.J. Stang and R.H. Summerville, J. Am. Chem. Soc., 91, 4600 (1969).

FIGURE 9



P. Stang, R. Summerville J.A.C.S, 91, 4600, 1969

Since then, the use of other sulfates and triflates has enabled experimenters to investigate numerous substitutions because of their excellence as a leaving group.

Element effects are negligible for the addition-elimination pathway because cleavage of the carbon to leaving group bond is not the rate determining step. Experimental evidence supports this idea.[22]

It should be noted that fluorine will give an enhanced rate but for different reasons. Because of fluorine's greater electronegativity, (F=4.0, Cl = 3.0, Br = 2.8)[23] it will increase the electronphilicity of

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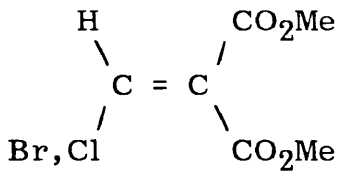
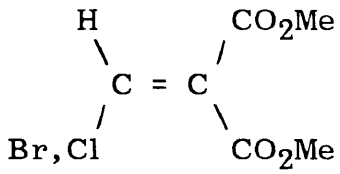
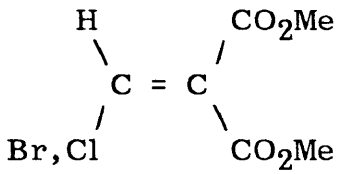
[22]Z. Rappoport and A. Topol, J. Chem. Soc., Perkin Trans. 2, 12, 1823 (1972).

[23]Pauling and Pauling, Chemistry, W.H. Freeman and Co., San Francisco, 1975, page 128.

the vinylic carbon and cause the rate-determining attack by the nucleophile to occur faster.

Table 2

nucleophile	substrate	K_{Br}/K_{Cl} @ 30°C
aniline		1.06
m-methoxyaniline		1.01
p-bromoaniline		1.05

Unlike the vinyl cation mechanism and the addition-elimination route, the concerted process is not as easily identified or modeled. Without an exemplary reaction to examine, it is impossible to know what element effects are observed for this mechanism. It is reasonably hypothesized that because the concerted process is between the extremes of the vinyl cation and the addition-elimination mechanisms that $k_{Br} > k_{Cl} > k_F$ and $k_{Otf} >> k_{Br}$. Departure of the leaving group is occur-

ring in the single rate determining step; however, because this is a bimolecular process where attack of the nucleophile is occurring simultaneously, the element effects should not be as pronounced as with vinyl cations. The electronegativities of the halide leaving groups will serve to moderate their rates because the slower leaving fluoride will again enhance the electrophilicity of the vinyl carbon atom. The expected result is still $k_{Br} > k_{Cl} > k_F$ but the magnitude of the ratio of rates may not be as great. Indeed, this trend has been recently observed for substitution in several lightly activated systems that are hypothesized to proceed via a concerted route.[24, 25]

FIGURE 10

$$PhCH{:}CHX + Co(dmgH)_2py^- \longrightarrow PhCH{:}CHCo(dmgH)_2py + X^-$$

$$I > Br > Cl > F$$

$$PhCH{:}CHX + Me_2CuLi \longrightarrow PhCH{:}CH_2 + PhCH{:}CHMe$$

$$k_{Br}/k_{Cl} \approx 100$$

and

$$k_F \longrightarrow 0$$

Both of the cited reactions involve a metal complex as the nucleophile. A great deal of interest has recently developed concerning the high nucleophilicity of these metal complexes.

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[24]D. Dodd, M. Johnson, B. Meeks, D. Titchnmarsh, K. Duong, and A. Gaudemer, J. Chem. Soc., Perkin Tras. 2, 1261 (1976).

[25]C. Maffeo, G. Marchese, and F. Naso, J. Chem. Soc., Perkin Trans. 1, 92 (1979).

Element effects give additional insight into which mechanism is functioning. Substitution via a vinyl cation intermediate gives the most pronounced element effects. Better leaving groups directly affect the rate and $k_{Br} >> k_{Cl} >> k_F$. When the addition-elimination mechanism is operating, element effects are negligible because cleavage of the leaving group bond does not occur in the rate determining step. It is hypothesized that a concerted substitution will show moderate element effects.

SECONDARY ISOTOPE EFFECTS

Secondary isotope effects result from isotopic substitution at a bond not being broken in the reaction. In the case of nucleophilic vinylic substitution a deuterium atom may be a substituent at either the α or the β-carbon and the resulting change in rate may be measured. The reaction coordinate is not affected by the deuterium substitution and so it makes no contribution to the isotope effect. Secondary isotope effects arise soley from the changes of zero point energies of ordinary vibrations which are dependent on mass. If a vibration's frequency decreases on going to the transition state then $k_H/k_D > 1$.[26] Conversely, if the vibrations frequency increases then $k_H/k_D < 1$. If the isotopic substitution is made at a carbon that undergoes a change of hybridization during the reaction, then the secondary isotope effects are often fairly pronounced.

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[26]A. Streitwieser, R. Jagow, R. Fahey, S. Suzuki, J. Am. Chem. Soc., **80**, 2326 (1958).

Because primary vinyl cations are not readily observed, there are not examples of α-secondary isotope effects immediately available. Rather, β and Γ secondary isotope effects as well as α isotope effects for solvolysis of halloallenes are known. Schiavelli, Ellis, Germroth, and Stubbs studied the solvolysis of various allenyl halides and observed their α and Γ isotope effects. The results indicate a larger than expected k_H/k_D.[27]

Table 3

SOLVOLYSIS OF BROMOALLENES

Substrate	Solvent	Temp	k_H/k_D
$Me_2C = C = CH(D)Br$	50% EtOH	54.2°C	1.20±.01
$Me_2C = C = CH(D)Br$	70% TFE	54.2°C	1.23±.02
$t\text{-}Bu_2C = C = CH(D)Br$	50% EtOH	74.4°C	1.28±.03
$t\text{-}Bu_2C = C = CH(D)Br$	70% EtOH	74.4°C	1.20±.01
t-Bu(Me)C = C = CH(D)Br	50% EtOH	64.2°C	1.20±.01
t-Bu(Me)C = C = CH(D)Br	70% EtOH	60.2°C	1.22±.01

In this case, an sp^2 hybridized carbon changes to an sp hybridized carbon as the allenyl cation intermediate is formed. The magnitudes of the α isotope effects are the largest ever reported for halide leaving groups. Schiavelli and Ellis estimated the maximum value for an α

[27]M. Schiavelli, T. Germroth, and J. Stubbs, J. Org. Chem., **41**, 681 (1976).

effect where there is an sp^2 - sp hybridization change from the exchange equilibrium constants shown.[28]

FIGURE 11

$$CH_3CH_3 + CH_2 = CHD \underset{}{\overset{}{\rightleftharpoons}} CH_3CH_2 + CH_2 = CH_2$$
$$K = 1.075$$

$$CH_2 = CH_2 + DC \equiv CH \underset{}{\overset{}{\rightleftharpoons}} CH_2 = CHD + H_C \equiv CH$$
$$K = 1.257$$

These equilibria imply that the isotope effect for sp^2 - sp hybridization is 1.257/1.075 = 1.17 times that for an sp^3 - sp^2 change. Assuming a maximum k_H/k_D = 1.125[29] for Br^- leaving from a saturated halide, then the maximum α isotope effect for solvolysis of a vinyl bromide is 1.17 X 1.125 = 1.32. This estimate agrees very well with the experimental value obtained for the solvolysis of $t\text{-}Bu_zC = C = CH(D)Br$ where k_H/k_D = 1.28.

Secondary isotope effects for substitutions proceeding via the addition elimination pathway have previously not been reported. If the deuterium analogues of primary vinyl halides that appear to undergo substitution by an addition-elimination route can be synthesized, then the isotope effect can be measured readily. Streitweiser[30] has predicted the maximum isotope effect is a result of the out of plane bending vibration that changes significantly for an sp^2 vs. an sp^3 carbon.

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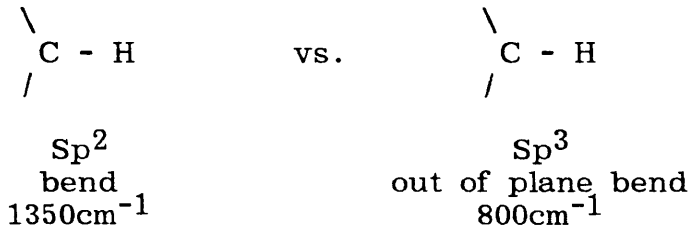
[28]M. Schiavelli and D. Ellis, J. Am. Chem. Soc., **95**, 7916 (1973).

[29]V. Shiner, J. Am. Chem. Soc., **90**, 418 (1968).

[30]Streitweiser, R. Jagow, R. Fahey, S. Suzuki, J. Am. Chem. Soc., **80**, 2326 (1958).

FIGURE 12



He predicts that the maximum isotope change will be $\frac{k_H}{k_D} = \exp\left[\frac{0.1865}{T}(1350\text{-}800)\right]$. At 298K this gives a maximum inverse effect of $k_H/k_D = .71$ if the transition state closely resembles an sp^3 hybridized carbon.

Determination of the α-secondary isotope effect should therefore be a very good tool for comparing mechanistic extremes. If substitutions proceeding by a vinyl cation mechanism give normal isotope effects and substitutions that occur by an addition-elimination route give inverse effects, then there is a distinct and observable difference that can be measured.

MECHANISTIC MODELS

In an attempt to model examples of each of the substitution routes, a number of ideal characteristics and compounds have been identified. The vinyl cation route has been the most thoroughly explored and explained. Substrates that undergo solvolysis by this mechanism are characterized by electron donating substituents that can stabilize the cationic intermediate. Entropies of activation are positive, as departure of the leaving group in the rate determining step leads to a

less ordered species. Leaving group effects are extremely pronounced with $k_{Br} >> k_{Cl} >> k_F$. Often times extraordinary leaving groups such as tosylates and triflates must by employed so that the cation may more readily be formed. With alkylvinyl triflates as substrates, β-deuterium isotope effects were found in all cases to be 20 - 60% larger than the corresponding effects of analogous saturated substrates. α-secondary isotope effects of various allenes that undergo substitution by an allenyl cation are small and positive (1.1 to 1.3).

At the other end of the mechanistic spectrum is the addition-elimination route. Substrates reported to undergo substitution by this mechanistic possibility are characterized by strong electron withdrawing groups on the β-carbon. Entropies of activation are highly negative because the system becomes more ordered as a bond forms from the nucleophile to the substrate in the rate determining step that occurs prior to departure of the leaving group. Leaving group effects are negligible because heterolytic dissociation of the leaving group occurs in the second rapid step. Secondary isotope effects are previously unobserved; however, they are predicted to be inverse with a maximum $k_H/k_D \approx .71$.

In the middle of the proposed continuum of mechanisms is the concerted process where bond formation to the nucleophile and bond breaking to the leaving group occur simultaneously. It is proposed that the stereochemical consequence of this single step substitution is retention of configuration and several examples of greater than 98% retention have been cited. However, retention is also a possibility for

addition-elimination and so by itself stereochemistry can not be used as the criterion for assigning observed reactions to this mechanism. In fact, there are no clear cut examples of substitution occurring by this mechanism. In an attempt to come up with a model system for a concerted process, investigators have turned to the oxidative - addition reactions of several transition metal complexes with vinyl halides.[31]

Stille and Lau[32] reviewed these reactions and more specifically addressed the oxidative addition of vinyl halides to transition-metal complexes. Most notably, these reactions proceed with "remarkable stereospecificity" which agrees with the suggestion that a concerted process will proceed with retention of configuration.[33]

FIGURE 13

$Pt[P(Ph)_3]_3$ + cis-β-bromostyrene $\longrightarrow$ $PtBr(HC = CHPh)(PPh_3)_2$

$Pt[P(Ph)_3]_3$ + trans-β-bromostyrene $\longrightarrow$ $PtBr(HC = CHPh)(PPH_3)_2$

A broadly examined complex is $Pt[P(Ph)_3]_4$[34] which will undergo an oxidative addition with a variety of substrates such as hydrogen halides, alkyl halides, vinyl halides and acetylenes. The platinum complex is a d^{10} compound and will react more readily and in milder conditions than similar reactions of d^8 compounds. The platinum complex first dissociates $Pt(PPh_3)_4$ to Pt $(PPh_3)_3$ + PPh_3. At this point, the

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[31]B. Mann, B. Shaw, N. Tucker, J. Chem. Soc., 2667 (1971).

[32]P. Stille and K. Lau, Accounts Chem. Res., 1977, **10**, 434.

[33]P. Fitton and J. McKeon, Chem. Commun., 4 (1968).

[34]J.P. Birk, J. Halpern, and A.L. Pickard, Inorg. Chem., **7**, 2672 (1968).

platinum has not undergone and oxidation as the triplenyl phosphine ligand is neutral and there is still no charge on the platinum; however, the platinum is now coordinatively unsaturated. The coordinatively unsaturated trigonal planar species is more reactive and will undergo an oxidative addition with an appropriate substrate. Pearson and Rajaran[35] observed the oxidative addition of methyl iodide to tetrakis (triphenyl phosphine) platinum (0) and hypothesized that dissociation of Pt $(PPh_3)_4$ to Pt $(PPh_3)_3$ was an important step before addition of the CH_3I. After the initial dissociation, the reaction is first order in both the alkyl halide and the platinum complex and appears to undergo a concerted oxidative addition.

$IrCl(CO)[P(C_6H_5)_3]_2$ is another compound that has a great tendency to add covalent molecules.[36] The iridium complex and some of its many reactions have been extensively studied by Vaska and the common name for this complex is Vaska's compound. In the mid-1960's R.F. Heck[37] reported the oxidative - addition of several alkyl halides to Vaska's compound and its rhodium analogue. Both of these d^8 complexes are converted into octahedral d^6 complexes as they undergo the oxidative addition of a covalent molecule to the coordination sphere. In particular, acyl halides add reversibly to the coordinatively unsaturated d^8 complexes and the reaction can be readily followed by the shift in the infrared band of the CO group to a higher frequency as the metal is

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[35]R. Pearson and C. Rajaram, Inorg. Chem., **13**, 246 (1976).

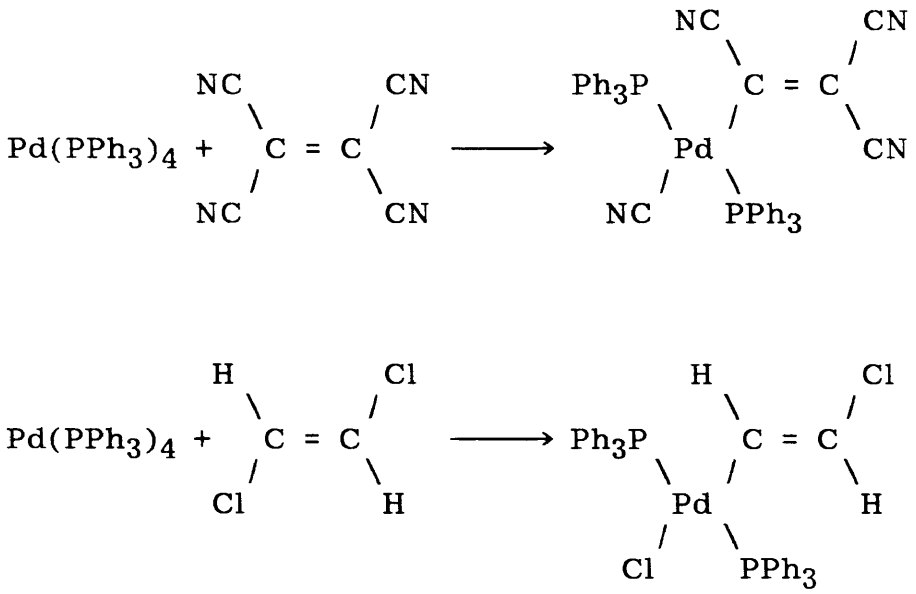
[36]Collman and Sears, Inorg. Chem., **7**, 27 (1968).

[37]R.F. Heck, J. Am. Chem. Soc., **86**, 2796 (1964).

oxidized and the degree of back bonding decreases.[38] These additions occur stereospecifically in agreement with the requirement for a concerted mechanism.

The addition of vinyl compounds to d^8 and d^{10} complexes is of particular interest because they can be thought of as a vinylic substitution by an excellent nucleophile rather than an oxidative addition. The facile addition of vinyl compounds to Pd $(PPh_3)_4$ was investigated by Fitton and McKeon.[39]

FIGURE 14



Once again, retention of configuration is observed and there is an initial dissociation of the tetrehedral platinum complex to a trigonal planer species.

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[38]R.F. Heck, J. Am. Chem. Soc., **86**, 2796 (1964).

[39]P. Fitton and J. McKeon, Chem. Commun., 4 (1968).

Johnson and Lewis[40] prepared other platinum and palladium complexes by the reaction of zero valent metal complexes ($M(PPh_3)_4$) with chlorinated olefins such as trichloroethylene and tetrachloroethylene. They characterized the metal complexes as excellent nucleophiles and their oxidative addition products were remarkably stable. The substitutions proceeded with retention of configuration and appeared to be the result of a concerted process.

The use of transition metal complexes as excellent nucleophiles may be the solution to finding a model system for the concerted process of nucleophilic vinylic substitution. These reactions proceed with great retention of configuration and appear to be first order in both substrate and nucleophile. More research is necessary to determine if these substitutions do indeed occur via a single-step mechanism.

We propose to measure the secondary isotope effects of several nucleophilic vinylic substitution reactions. These isotope effects and other known reaction characteristics should enable the experimenter to predict which mechanism is functioning, or approximately where along the mechanistic continuum a particular reaction lies.

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[40]B. Johnson, J. Lewis, J. Jones and K. Taylor, J. Chem. Soc., Dalton Trans., **34** (1974).

EXPERIMENTAL

All temperature measurements are uncorrected. Infrared spectra were measured with a Perkin-Elmer 1320 spectrophotometer and nmr spectra with a Varian FT-80A instrument; signal positions are given in delta units downfield from tetramethylsilane.

Solvents.

Laboratory grade methylene chloride (Fisher, D-37) was distilled over phosphorous pentoxide under a nitrogen atmosphere, and stored over Lind 4-A molecular sieves. U.V. grade acetonitrile (Burdick and Jackson) was used without further purification although care was taken to avoid moisture after the bottles were opened. Diethyl ether (Fisher, laboratory grade) and methanol (Fisher) were used without purification.

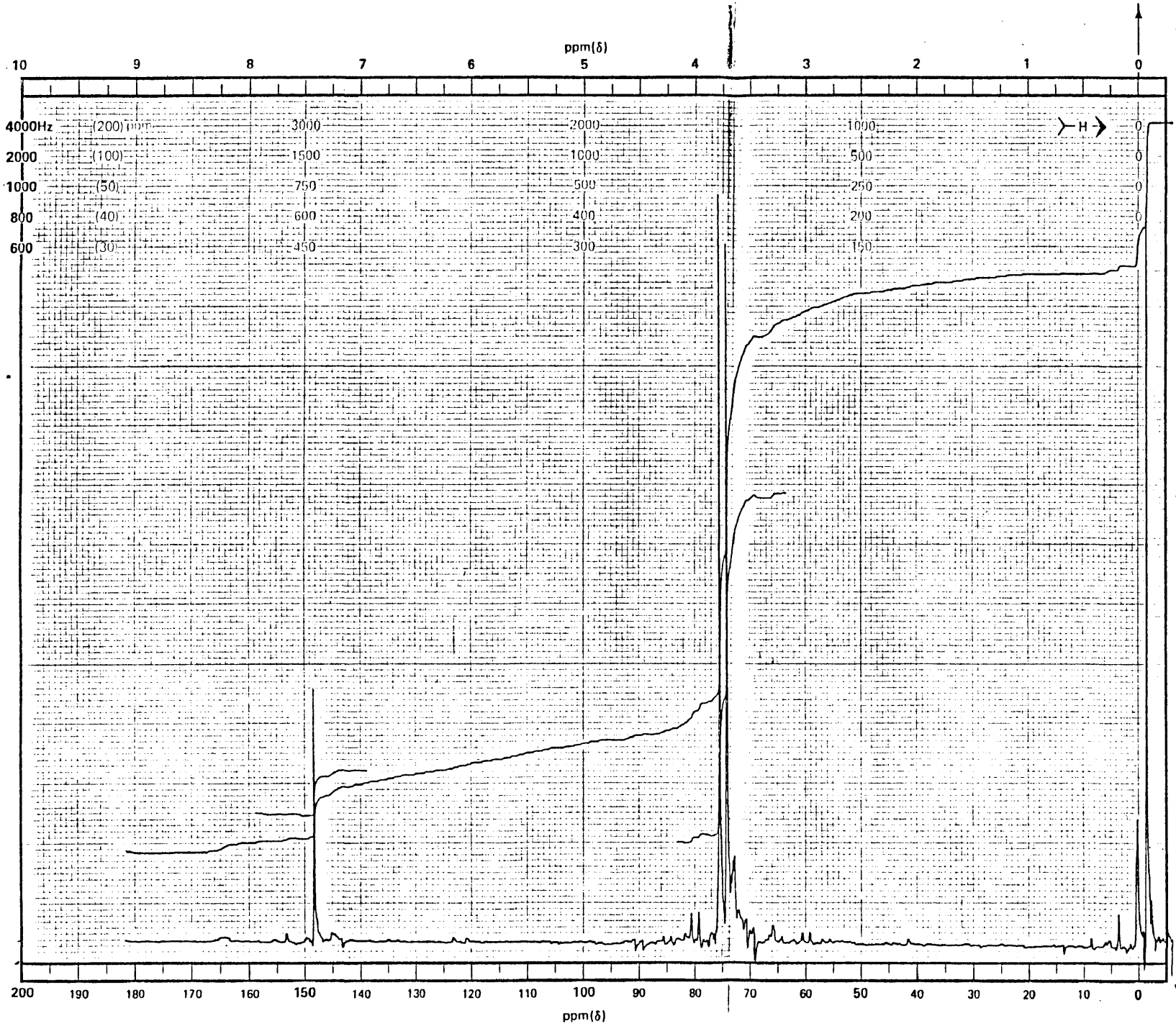
Materials.

1-chloro-2,2-dimethoxycarbonylethylene, b.p. 109°C/20 mm Hg was prepared from the sodium salt of dimethyl hydroxymethylenemalonate (prepared by the successive addition of 0.5 mole sodium methoxide and 1.0 mole methyl formate to a solution of 0.5 moles of dimethyl malonate in 150 ml of methanol. The mixture was allowed to reflux for 90 minutes then cooled slowly. Fine white crystals of the salt were collected on a Buchner funnel and washed with petroleum ether.) and one equivalent of

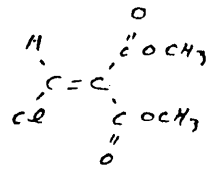
phosphorus pentachloride. A slurry of the salt in methylene chloride was allowed to reflux for four hours while the phosphorus pentachloride was slowly added. The reaction mixture was poured into ice water and the organic layer was washed three times with equal volumes of distilled water and then twice with 10% sodium bicarbonate. After drying with magnesium sulfate the product mixture was distilled on a 20 cm vigreaux column to give the desired product as a colorless liquid; 3.8δ(6H, 2s, 2Me) and 7.4δ(1H, s, H-C:).

1-bromo-2,2-dimethoxycarbonylethylene, b.p. ~16°C/6mm Hg was prepared analogously to its 1-chloro derivative with the following exceptions. One equivalent of phosphorus tribromide and one equivalent of bromine were added to a slurry of the sodium salt of dimethyl hydroxymethylenemalonate in methylene chloride. Again, the reaction mixture was allowed to reflux for four hours and was purified as before. Gas chromatographic analysis of the final product on a 30 meter methylsilicone capillary column revealed that the product was only about 70% pure. Subsequent attempts to purify the product by preparative gas chromatography were futile because the product appeared to decompose on the column.

1-chloro-1-deutero-2,2-dimethoxycarbonylethylene was prepared analogously to its protio derivative with the exception that methyl--d-formate (Aldrich, gold label) was used in place of the protio methyl formate. G.C. analysis revealed the product to be ~98% pure; δ3.84 (6H, 2s, 2Me) with essentially negligible protio contamination.



CFT-20
SPECTRUM NO. _____
OPERATOR SKF DATE 8/22/84
SAMPLE _____
TUBE OD: 5mm ☑ 8mm ☐ 10mm ☐ ____ ☐



NUCLEI: ^{1}H ☑ ^{13}C ☐ ^{19}F ☐ ^{31}P ☐ ____ ☐
LOCK ☑ INTERNAL ☐ EXTERNAL
LOCK SIGNAL $CDCl_3$
SPIN RATE 25 rps. TEMP ____ °C

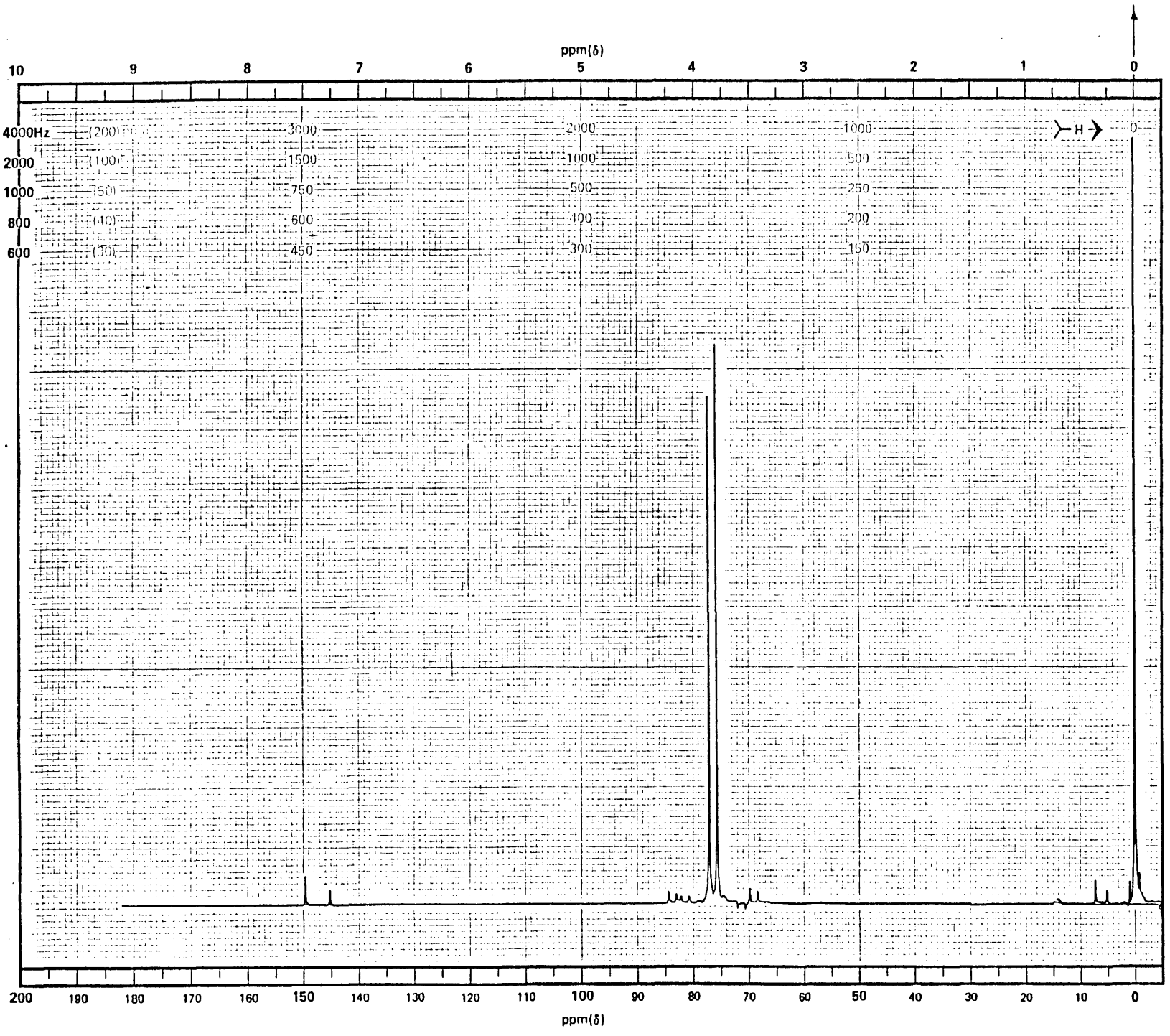
ACQUISITION
SPECTRAL WIDTH (SW) 1000 Hz
NO. OF TRANSIENTS (NT) 1
ACQUISITION TIME (AT) 8.191 sec.
PULSE WIDTH (PW) 30 μ sec.
PULSE DELAY (PD) 0 sec.
DATA POINTS (DP) 16384

TRANSMITTER OFFSET (TO) 44
HIGH FIELD _____ LOW FIELD _____
RECEIVER GAIN (RG) 4

DECOUPLER MODE (DM) 0
DECOUPLER OFFSET (DO) 54
NOISE BANDWIDTH (NB) 2000 kHz
ACQUISITION MODE (AM) 0

DISPLAY
SENS. ENHANCEMENT (SE) 0 sec.
WIDTH OF PLOT (WP) 800 Hz
END OF PLOT (EP) 260 Hz
WIDTH OF CHART (WC) 800 Hz
END OF CHART (EC) 0 Hz
VERTICAL SCALE (VS) 120
REFERENCE LINE (RL) 0

WILMAD GLASS CO., INC.
U.S. Route 40 and Oak Road
BUENA, N.J. 08310 U.S.A.
Printed in U.S.A. 1-79/100/WP CHART NO. WCV-20



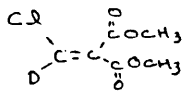
CFT-20 ____

SPECTRUM NO. ____

OPERATOR P.F.D. DATE 1-28-86

SAMPLE ____

TUBE OD: 5mm☐ 8mm☐ 10mm☐ ____☐



previously prepared

NUCLEI: ^{1}H☒ ^{13}C☐ ^{19}F☐ ^{31}P☐ ____☐

LOCK ☐INTERNAL ☐EXTERNAL

LOCK SIGNAL ____

SPIN RATE 25 rps. TEMP ____ °C

ACQUISITION

SPECTRAL WIDTH (SW) 1000 Hz

NO. OF TRANSIENTS (NT) 5

ACQUISITION TIME (AT) 8.191 sec.

PULSE WIDTH (PW) 30 μ sec.

PULSE DELAY (PD) 0 sec.

DATA POINTS (DP) 16,382

TRANSMITTER OFFSET (TO) 44

HIGH FIELD ____ LOW FIELD ____

RECEIVER GAIN (RG) 3

DECOUPLER MODE (DM) 0

DECOUPLER OFFSET (DO) 56

NOISE BANDWIDTH (NB) -3000 kHz

ACQUISITION MODE (AM) 0

DISPLAY

SENS. ENHANCEMENT (SE) 0 sec.

WIDTH OF PLOT (WP) 800 Hz

END OF PLOT (EP) -75.191 Hz

WIDTH OF CHART (WC) 800 Hz

END OF CHART (EC) 0 Hz

VERTICAL SCALE (VS) 164

REFERENCE LINE (RL) 0

WILMAD GLASS CO., INC.
U.S. Route 40 and Oak Road
BUENA, N.J. 08310 U.S.A.

Printed in U.S.A. WP-1/80-100 CHART NO. WCV-20

1-bromo-1-deutero-2,2-dimethoxycarbonylethylene was prepared analogously to its protio derivative and the deuterated chloro-compound. G.C. analysis revealed the product to be ~95% pure.

Aniline and derivatives (2,6-dimethylaniline, m-anisidine and p-bromoaniline) were distilled over phosphorus pentoxide and then stored over molecular sieves.

Tetrakistriphenylphosphineplatinum(0) was purchased from the Aldrich Chemical Company and used without further purification. Care was taken not to expose the platinum complex to air, sunlight, or moisture. Solutions of the complex in acetonitrile were prepared in a dry box and stored under a nitrogen atmosphere.

Kinetic Procedure.

Stock solutions of the nucleophiles were prepared weekly. The nucleophile solution was carefully pipetted into each of the conductance cells and allowed to equilibrate to the desired temperature in a constant temperature bath for twenty minutes to an hour. From two to five μL of the appropriate substrate solution (~0.100M) were injected into the sealed cells so that there was at least a fifty fold excess of nucleophile. For example, if 5μL of a .100 M substrate solution were injected into 15 ml of a 1.67×10^{-4}M nucleophile solution, then there would be the desired 50 fold excess of nucleophile.

The reaction was followed using a Hewlett-Packard 4274-A multi-frequency LCR 9826 computer with a quartz clock. One hundred or more

points were taken over four to five half lives. The pseudo-first order rate coefficients in the presence of excess nucleophile were calculated with the aid of the KINETICS program.[41] The correlation coefficients were >0.99 and k_{obs} values were obtained by dividing the first-order rate coefficients by the concentration of the nucleophile.

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[41]This program was written by Schiavelli and Huey for this specific application.

RESULTS AND DISCUSSION

The reaction of several aniline derivatives with 1-chloro-2,2-dimethoxycarbonylethylene was chosen as a reaction that was hypothesized to proceed via an addition-elimination route.[42] Several facts support this idea: $\Delta S^{\ddagger} \approx -40$ cal/mol•K,[43] $k_{Cl}/k_{Br} \approx 1$, and the electron withdrawing substituents on the β-carbon will readily support a zwitterion. Table 4 shows the observed rates as well as the concentration of both nucleophile and substrate, and the number of runs. The observed rates agree well with previously measured rates for these reactions. Rappoport reported $k_{obs} = .00631 \pm .00021$ for the reaction of 2,6-dimethylaniline and we observed a rate of $k_{obs} = .00644 \pm .00020$ for the same reaction.

Similarly, with the reaction of the same nucleophiles with 1-chloro-1-deutero-2,2-dimethoxycarbonylethylene was observed and recorded in Table 5.

Table 6 shows the secondary isotope quotient for these reactions.

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[42]Z. Rappoport and A. Topol, J. Chem. Soc., Perkin Trans. 2, **12**, 1923 (1972).

[43]"The Chemistry of the Amino Group," Interscience Publishers, London, 1968, page 128.

Table 4

REACTION OF 1-CHLORO-2,2-DIMETHOXYCARBONYLETHYLENE WITH:

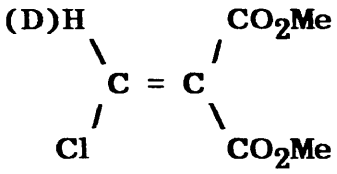
Nucleophile	Concentration of Nucleophile	Substrate	Number of Runs	Temperature	$K_{observed}$ (L/mol•s)
aniline	5.11mM	0.104mM	5	25.10±.08°C	.07392±.00139
2,6-dimethylanine	5.12mM	0.104mM	5	24.81±.10°C	.00644±.00020
m-anisidine	5.12mM	0.104mM	5	25.12±.08°C	.05858±.00336
p-bromoaniline	5.06mM	0.104mM	5	25.05±.18°C	.03130±.00090

Table 5

REACTION OF 1-CHLORO-1-1DEUTERO-2,2-DIMETHOXCARBONYLETHYLENE WITH:

Nucleophile	Concentration of Nucleophile	Number of Substrate	Runs	Temperature	$K_{observed}$ (L/mol•s)
aniline	5.11mM	0.104mM	5	25.09±.09°C	.1013±.0025
2,6-dimethylanine	5.12mM	0.104mM	4	24.90±.12°C	.00814±.00046
m-anisidine	5.12mM	0.104mM	4	25.10±.10°C	.07934±.00097
p-bromoaniline	5.06mM	0.104mM	5	25.05±.15°C	.03827±.00034

Table 6

REACTION OF  WITH:

Nucleophile	k_H/k_D
aniline	.730 ±.032
2,6-dimethylaniline	.791 ±.069
m-anisidine	.739 ±.050
p-bromoaniline	.818 ±.030

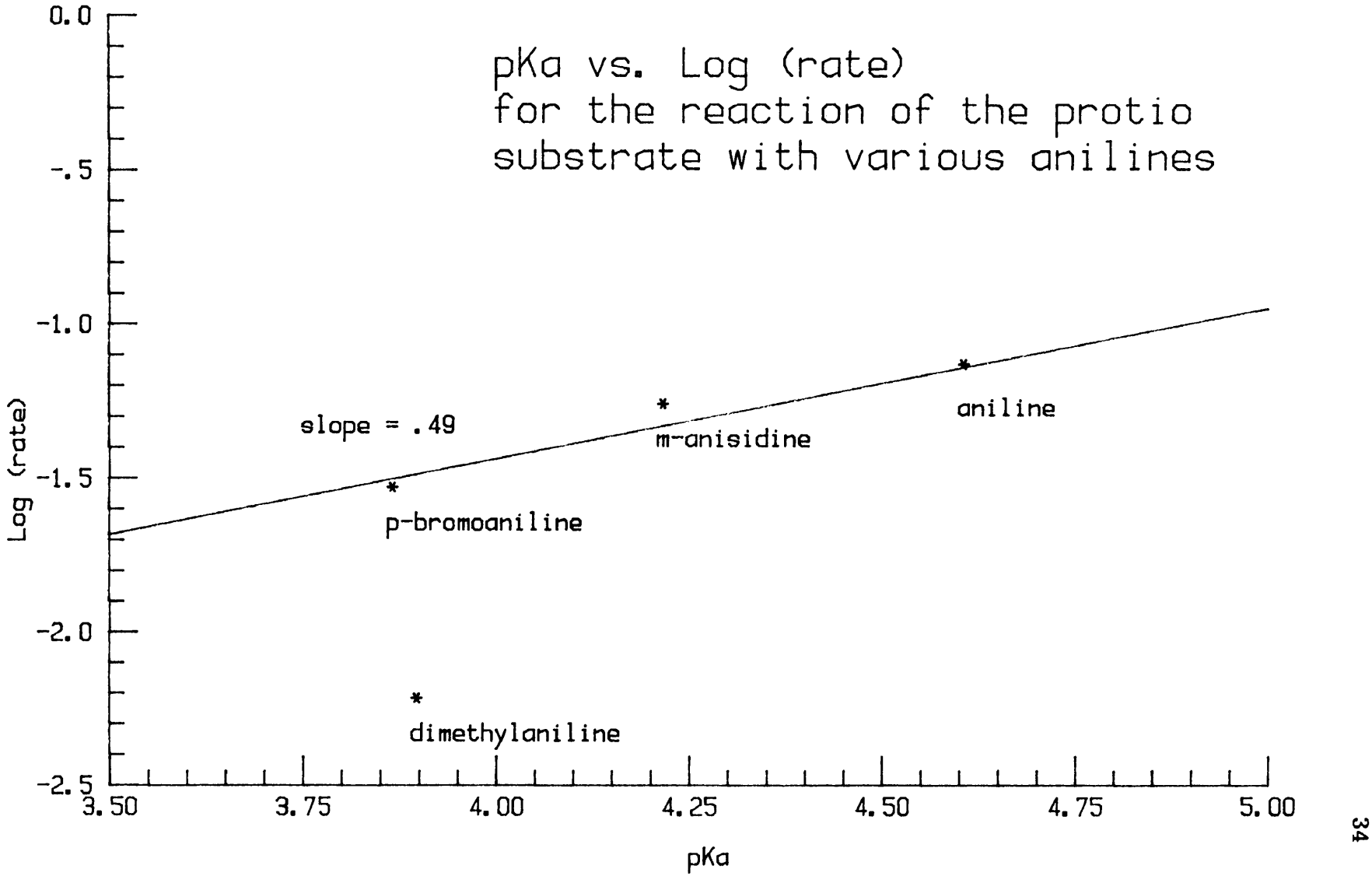
There is a distinct correlation between the observed rates for the various amines and their recorded pK_a values.

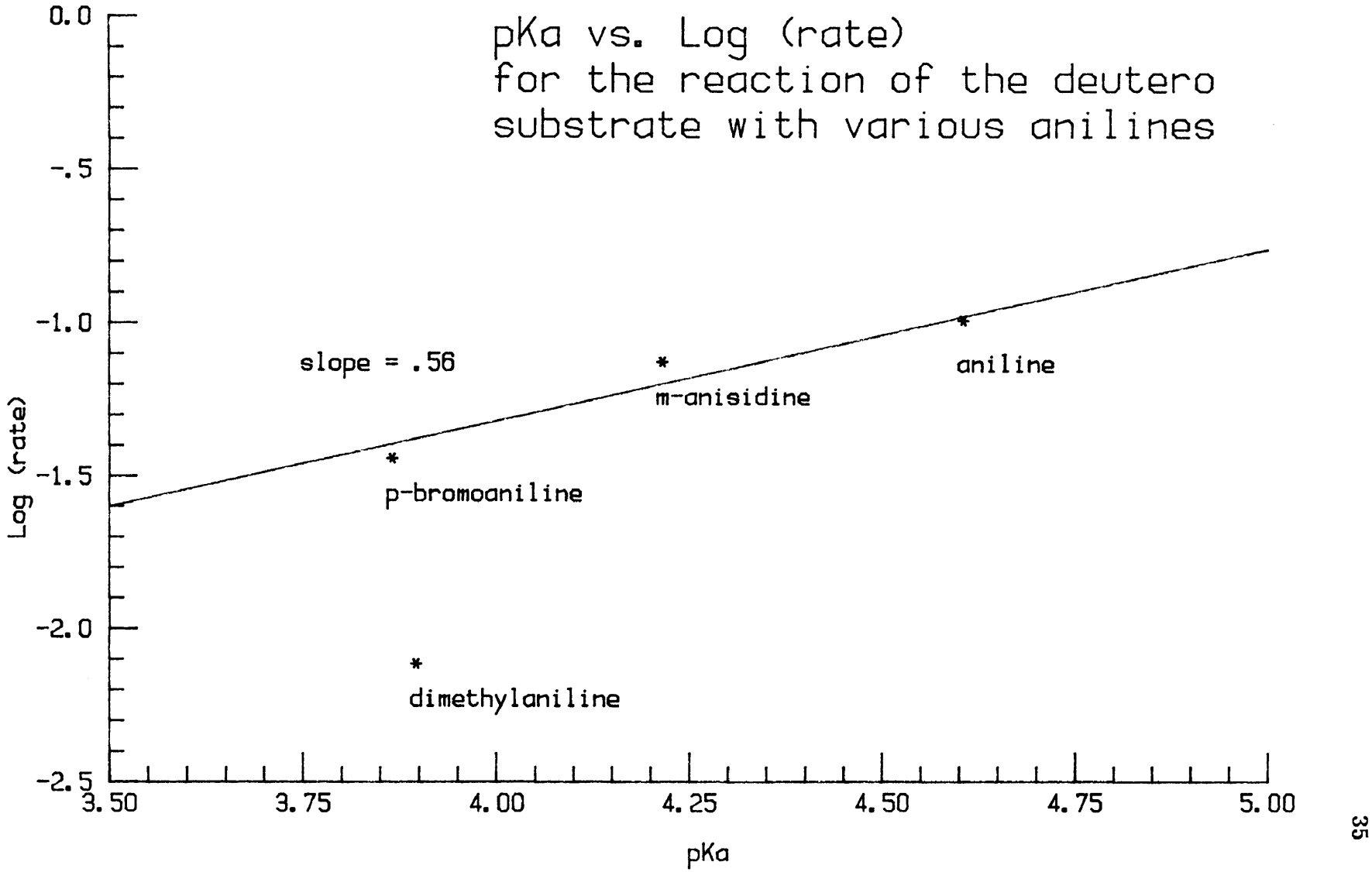
Table 7

pK_a VALUES OF ANILINE AND DERIVATIVES

Nucleophile	pK_a*
aniline	4.60
2,6-dimethylaniline	3.89
m-anisidine	4.21
p-bromoaniline	3.86

*"The Chemistry of the Amino Group," Interscience Publishers, London 1968.


pKa vs. Log (rate)
for the reaction of the protio
substrate with various anilines
0.0
-.5
-1.0
-1.5
-2.0
-2.5
Log (rate)
slope = .49
p-bromoaniline
m-anisidine
aniline
dimethylaniline
3.50
3.75
4.00
4.25
4.50
4.75
5.00
pKa


pKa vs. Log (rate)
for the reaction of the deutero
substrate with various anilines
0.0
-.5
-1.0
-1.5
-2.0
-2.5
Log (rate)
slope = .56
aniline
m-anisidine
p-bromoaniline
dimethylaniline
3.50
3.75
4.00
4.25
4.50
4.75
5.00
pKa

Aniline has the highest pK_a and exhibits the fastest rate. The rates of m-aniside and p-bromoaniline decrease proportionally as there pK_a values also decrease. It should be noted that 2,6-dimethylaniline does not follow this general trend. Its rate is slowed considerably compared to p-bromoaniline which has an almost identical pK_a value. This is readily explained by steric hindrance on the rate of attack by the amino nitrogen.

These results also agree extremely well with theoretical calculations of Streitweiser[44] and Strausz[45] for a reaction where an sp^2 carbon is transformed to an sp^3 carbon in the transition state. Their calculated values for the maximum inverse secondary isotope effect are 0.71 and 0.72, respectively. These isotope effects, coupled with the previously reported physical constants, suggest that this is a reaction proceeding by the addition-elimination mechanism and that bond formation from the nucleophile to carbon is nearly complete before any dissociation of the leaving group begins. If the calculations of Streitweiser and Strausz are correct, then the reactions of aniline and m-anisidine appear to be very close to the mechanistic extreme of addition-elimination. Furthermore, these results do indicate a distinct and observable difference between the extremes of the addition-elimination and vinyl cation route.

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[44]A. Streitwieser, R. Jagow, R. Fahey, S. Suzuki, J. Am. Chem. Soc., **80**, 2326 (1958).

[45]O. Strausz, I. Safarik, W. O'Callaghan, and H. Gunning, J. Am. Chem. Soc., **94**, 1828 (1972).

With these new observations and the previous hypothesis that certain transition metal complexes might proceed by a concerted substitution, a preliminary investigation was begun to determine if a reaction that did proceed via a single step process could be observed. Specifically, this investigation would focus on the observed secondary isotope effects for such a reaction in the hope that a relationship between secondary isotope effects and mechanism could be observed.

Tetrakistriphenylphosphineplatinum(0) was suggested as the nucleophile because of its high degree of nucleophilicity and the previous observation that it gave retention of configuration in its reactions with cis and trans-β-bromostyrene.[46] The reaction of tetrakistriphenylphosphineplatinum(0) with 1-chloro-2,2-dimethoxycarbonylethylene was followed by the same kinetic procedure as before. Table 8 reports the observed rates at three different temperatures.

Table 8

REACTION OF $Pt[P(Ph)_3]_4$ WITH 1-CHLORO-2,2-DIMETHOXYCARBONYLETHYLENE:

Number of Runs	$Pt[P(Ph)_3]_4$	Substrate	Temperature	$k_{observed}$ (L/mol•s)
6	1.046mM	.0191mM	14.75±.10°C	.0942±.0071
4	1.051mM	.0191mM	25.32±.03°C	.2112±.0038
4	1.046mM	.0191mM	34.95±.01°C	.3456±.0198

[46]P. Fitton and J. McKeon, Chem. Commun., 4 (1968).

Similarly, the reaction of tetrakistriphenylphosphineplatinum(0) with 1-chloro-1-deutero-2,2-dimethoxycarbonylethylene was observed and the appropriate data is reported in Table 9. Table 10 shows the secondary isotope effects for these reactions at the various temperatures.

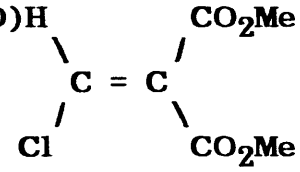
Table 9

REACTION OF $Pt[P(Ph)_3]_4$ WITH 1-CHLORO-1-DEUTERO-2,2-DIMETHOXYCARBONYLETHYLENE

Number of Runs	$Pt[P(Ph)_3]_4$	Substrate	Temperature	$k_{observed}$ (L/mol•s)
5	1.046mM	.0185mM	14.75±.10°C	.1215±.0171
4	1.051mM	.0185mM	25.32±.03°C	.3620±.0117
4	1.046mM	.0185mM	34.95±.01°C	.6582±.0452

Table 10

REACTION OF $Pt[P(Ph)_3]_4$ WITH



Temperature	k_H/k_D
14.75±.10°C	.775 ±.167
25.32±.03°C	.583 ±.029
34.95±.01°C	.525 ±.065

These large inverse isotope effects suggest an entirely different mechanism is operating. A plot of the natural logarithm versus the inverse of the absolute temperature gives a line whose slope is equal to $-E_a/R$ according to the Arrenius equation.[47] Figures 19 and 20 show a plot of Ln(k) versus 1/T for both the protio and deutero compounds. Once E_a is calculated, $\Delta S^{\ddagger}$ and $\Delta H^{\ddagger}$ can be found by the following equations.[48]

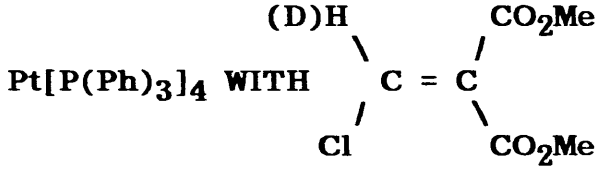
$$Ea = \Delta H^{\ddagger} + RT$$

$$\Delta S^{\ddagger} = \frac{\Delta H^{\ddagger}}{T} + 4.58 \log \frac{k}{T} - 47.4$$

Using these equations and the previously reported data, the following parameters are reported in Table 11.

Table 11

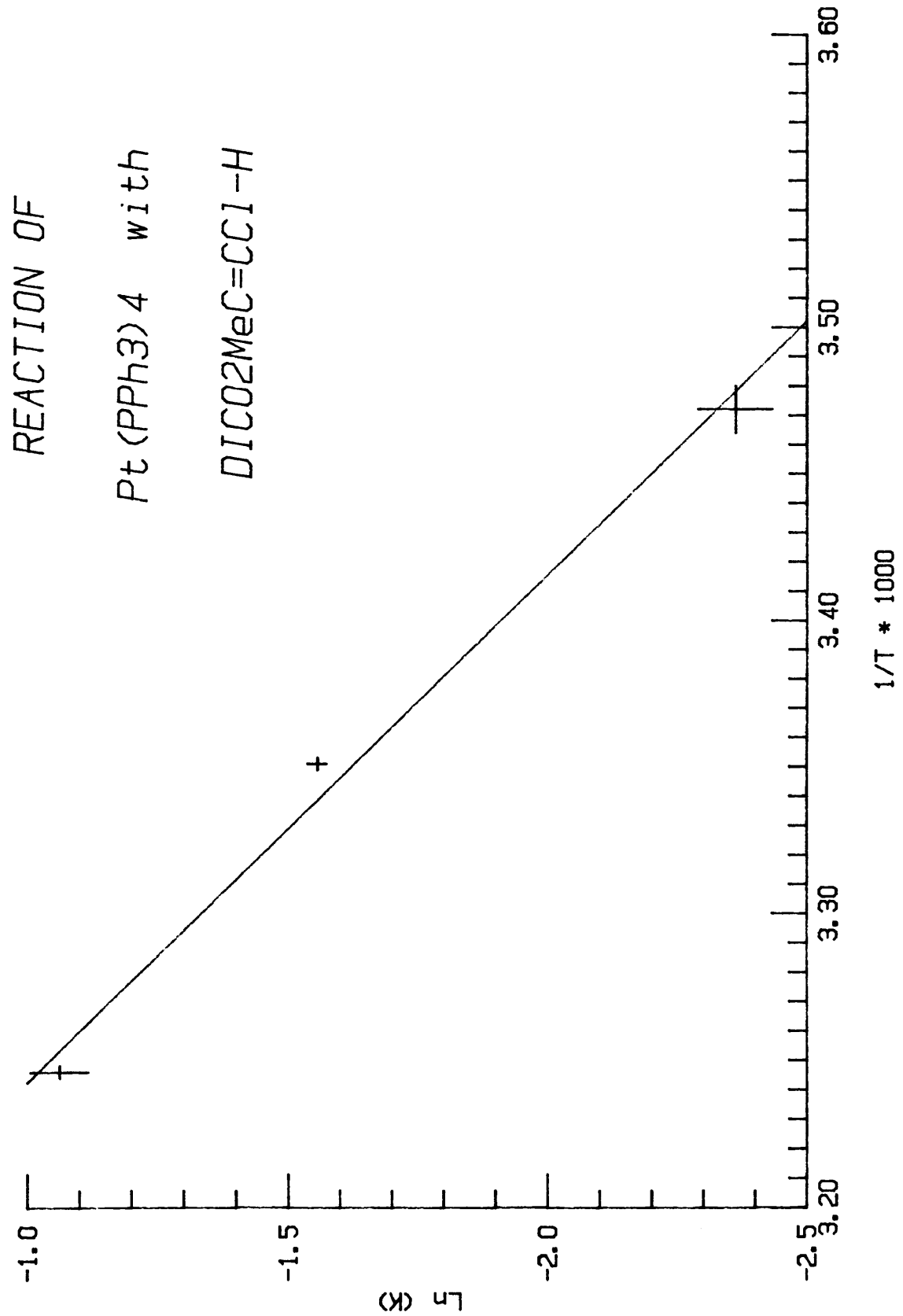
PHYSICAL PARAMETERS FOR THE REACTION OF

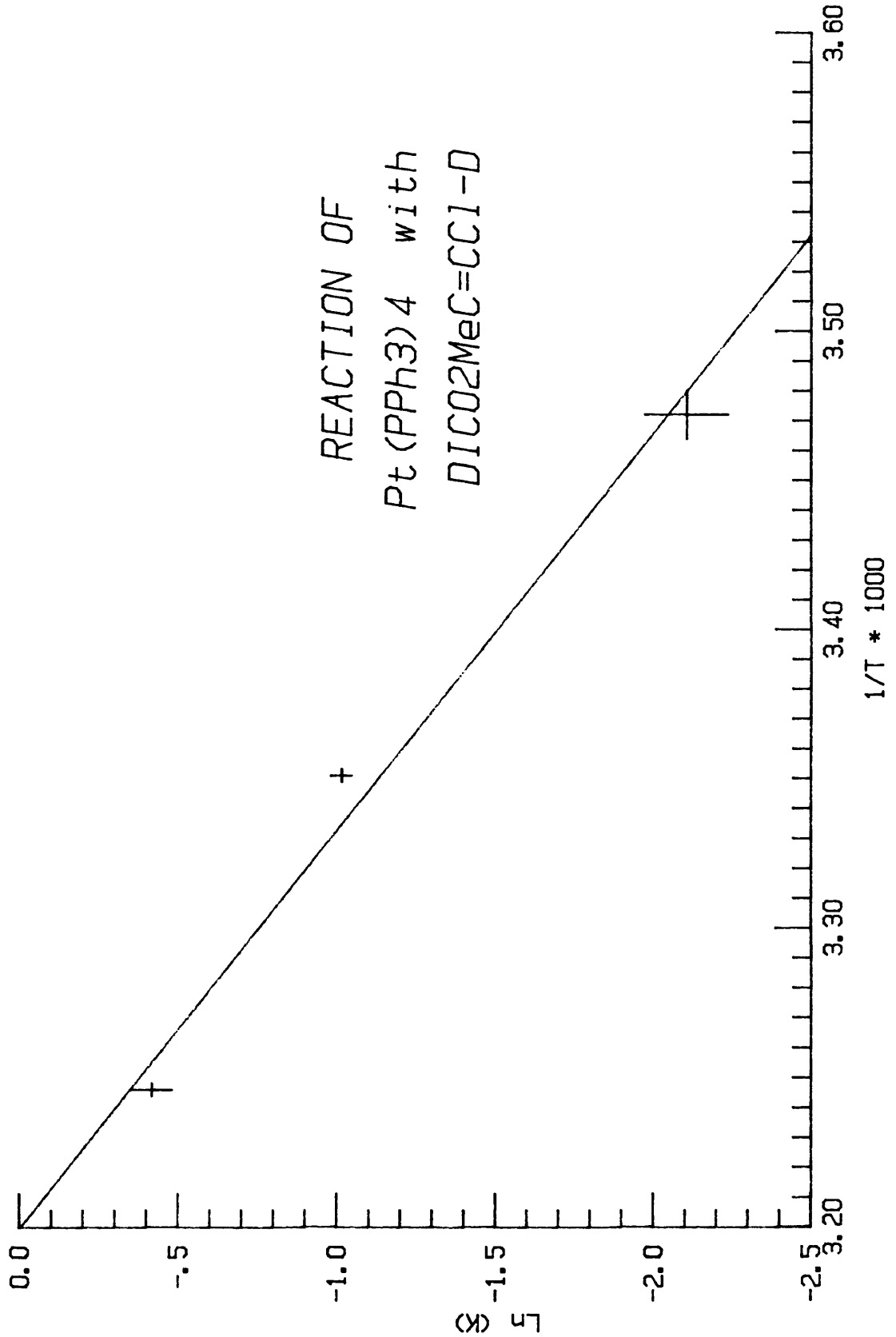


Substrate	Ea $\frac{Kcal}{mol}$	$S^{\ddagger}$ $\frac{cal}{mol \cdot K}$	$\Delta H^{\ddagger}$ $\frac{Kcal}{mol}$
protio	11.5	-44.0	10.9
deutero	14.9	-30.1	14.3

[47] W. Carey and H.Sundberg, "Advanced Organic Chemistry," Plenum Press, New York, 1985.

[48] W. Carey and H.Sundberg, "Advanced Organic Chemistry," Plenum Press, New York, 1985.

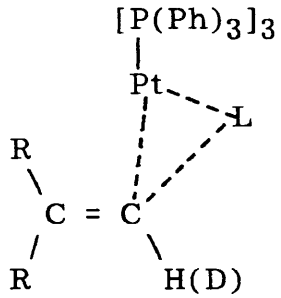

REACTION OF
Pt(PPh3)4 with
DICO2MeC=CCl-H
-1.0
-1.5
-2.0
-2.5
Ln (K)
3.20
3.30
3.40
3.50
3.60
1/T * 1000


REACTION OF
Pt(PPh3)4 with
DICO2MeC=CCl-D
0.0
-.5
-1.0
-1.5
-2.0
-2.5
ln (K)
3.20
3.30
3.40
3.50
3.60
1/T * 1000

There are several possibilities to explain the large inverse isotope effect. The size of the platinum complex must be considered. Steric effects will contribute to a secondary isotope effect and the platinum complex is clearly much larger than the nucleophiles that had previously been used (i.e., aniline and methoxide ions). Another possible explanation of the large inverse isotope effects might be that another mechanism is functioning.

Figure 21

PROPOSED TRANSITION STATE FOR THE SUBSTITUTION REACTION OF TRIKISTRIPHENYLPHOSPHILE PLATINUM WITH VINNYLIC SUBSTRATES



If the platinum inserts itself into the carbon-halide bond there will be greater restriction around the carbon and a more pronounced isotope effect. It does appear that the platinum complex dissociates from the tetrakis to the tris species before it reacts.[49] If this is the case, then it is possible that the now coordinatively unsaturated metal is inserted directly between the carbon and halide. The three-membered cyclic transition state would have partial bond character between the platinum, carbon and halide. To further investigate this

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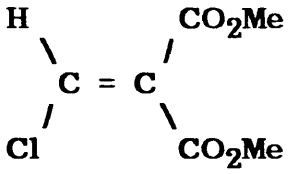
[49]M. Kowalski and P. Stang, personal communication.

possibility a preliminary observation of leaving group effects was undertaken. The reaction of 1-chloro-1-deutero-2,2-dimethoxycarbonylethylene and its bromo analogue with the platinum complex was observed. Preliminary results indicate that $k_{Cl}/k_{Br} \approx 3$. This is even more puzzling, because it suggests that cleavage of the stronger bond (C-Cl) is occurring faster than dissociation of the weaker bromine bond.

The entropies and enthalpies of activation for the reaction of the platinum complex with both the deuterated and protio substrate correspond very well to those reported for the reaction of aniline derivatives with the same substrate.

Table 12

REACTION OF  WITH:

	$\Delta S^{\ddagger}$ $\frac{cal}{mol \cdot K}$	$\Delta H^{\ddagger}$ $\frac{Kcal}{mol}$
analine[50]	-40	7.3
$Pt[P(Ph)_3]_4$	-44	10.9

This would seem to indicate that the reaction is proceeding via an addition-elimination mechanism. It is not readily apparent how to

[50]Z. Rappoport and A. Topol, J. Chem. Soc., Perkin Trans. 2, **12**, 1923 (1972).

addition-elimination route with the preliminary observation that $k_{Cl}/k_{Br} \approx 3$. Clearly leaving group effects of this magnitude are not associated with addition-elimination substitution.

More research is needed to determine which mechanism is functioning when the platinum complex undergoes nucleophilic attack on such an activated substrate. It is reasonable to suppose that the substitution is proceeding with some bond formation to the nucleophile prior to bond dissociation to the leaving group; however, other complicating factors cannot be ignored. The dissociation of the platinum complex does allow for the possibility of direct insertion or some other mechanistic consideration.

In the search for the direct substitution or concerted process, other substrates must be investigated. The use of less activated substrates coupled with better leaving groups might provide the necessary combination to observe such a one step process. The reaction of isobutenyltriflate with the platinum complex is proposed as a sufficiently deactivated substrate with an excellent leaving group that should readily undergo nucleophilic attack by the platinum complex. The availability of measuring a secondary isotope effect at the α-carbon makes the investigation of this reaction even more interesting and necessary to understanding the relationship between secondary isotope effects and where along the mechanistic continuum a particular substitution reaction lies.

VITA

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